SCIENTIFIC SECTION

Original Articles

Intranasally administered phenylephrine and blood pressure

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The possibility that intranasally administered phenylephrine might cause systemic vasoconstriction and an important increase in blood pressure if administered to susceptible individuals in higher doses was investigated in two groups potentially at high risk: 12 patients with chronic nasal congestion whose blood pressure was normal and 14 patients with hypertension receiving the β-blocker metoprolol. On two separate days increasing doses (0.5 to 4 mg) of phenylephrine or a placebo of identical appearance were instilled into the nostrils at hourly intervals. The blood pressure and the heart rate were recorded every 10 minutes. The total amount of phenylephrine administered (7.5 to 15 mg) was 4 to 30 times the manufacturer's recommended dose. No significant changes in blood pressure or heart rate occurred in either group after the instillation of phenylephrine.

On a étudié chez deux groupes à risque élevé potentiel la possibilité que l'administration intranasale de phényléphrine cause une vasoconstriction générale et une importante augmentation de la tension artérielle lorsqu'elle est donnée à doses plus fortes à des sujets sensibles. Ces deux groupes étaient composés de 12 patients souffrant de congestion nasale chronique et dont la tension artérielle était normale, et de 14 hypertendus recevant le médicament β-bloquant métoprolol. Lors de deux jours séparés des doses croissantes (de 0.5 à 4 mg) de phényléphrine ou un placebo d'apparence identique furent instillés dans les narines à intervalles d'une heure. La tension artérielle et le rythme cardiaque furent enregistrés à toutes les 10 minutes. La quantité totale de phényléphrine qui fut administrée (7.5 à 15 mg) représente de 4 à 30 fois la dose recommandée par le fabricant. Aucun changement significatif de tension artérielle ou de rythme cardiaque n'est apparu chez l'un ou l'autre groupe après l'instillation de phényléphrine.

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Topical nasal decongestants shrink edematous nasal mucosa by producing local arteriolar constriction. The active ingredient in many of these preparations is an α-adrenoceptor agonist with vasoconstrictor properties. Absorption of this agent into the systemic circulation is possible, and this could theoretically cause generalized arteriolar vasoconstriction and a pressor response. Since nasal decongestants are widely available "over the counter", it is important to know if they do indeed increase the blood pressure.

This knowledge has become especially important since the introduction of β-adrenoceptor blocking drugs for treating conditions such as hypertension and angina. A recent report has suggested that patients receiving such therapy may be especially prone to a rise in blood pressure following intraocular administration of an α-adrenoceptor agonist.[1] Theoretically, β-adrenoceptor blockade may leave α-adrenoceptor activity unopposed in the arteriolar smooth muscle, predisposing the patient to exaggerated vasoconstriction in response to the exogenous α-adrenoceptor agonist. If this supposition is true, many patients receiving β-blockers may be at risk of a rise in blood pressure if they receive topical therapy with vasoconstricting agents.

We examined the possible pressor effect of phenylephrine, a drug that is widely used as both a nasal decongestant and a mydriatic. We expected that intranasally administered phenylephrine would not produce a clinically important increase in blood pressure because of insufficient absorption from the nasal mucosa.

Subjects and methods

The study population included 12 patients (mean age 27.7 years) with chronic nasal congestion secondary to conditions such as allergic rhinitis whose blood pressure was normal and 14 patients with hypertension (mean age 53.4 years) who were receiving long-term therapy with metoprolol (mean daily dose 185.7 mg). The first group was recruited from the office practice of an allergist and the second from the hypertension clinic at Sunnybrook Medical Centre, Toronto. Entry criteria included a diastolic blood pressure of less than 100 mm

Hg with the patient supine, no known secondary causes for hypertension, a serum creatinine level of less than 220 μmol/l (2.5 mg/dl) and no evidence of active cardiovascular or cerebrovascular disease. Informed consent was obtained from each patient.

After not receiving any vasoconstrictor substances for 24 hours, the patients were studied in the quiet surroundings of the hypertension unit between 8 am and 5 pm on 2 days at least 1 week apart. They were given phenylephrine hydrochloride (Neo-Synephrine, Winthrop Laboratories) or an identical placebo solution on separate days, with the order of the drug and placebo randomized. The study design was double-blind, and the code identifying each solution was kept on file in the department of pharmacy. The blood pressure (systolic and phase 5 diastolic) was measured by a specially trained nurse using a Hawksley Random Zero sphygmomanometer (Hawksley Instruments Ltd., Sussex, England), and the cardiac rhythm was monitored continuously on an electrocardiograph oscilloscope.

Each day, after a minimum rest of 30 minutes, the patients received two drops of placebo in each nostril to familiarize them with the procedures. The blood pressure and heart rate were recorded for 1 hour. Thereafter, the drug or placebo solution was administered in increasing doses at hourly intervals. The patients with nasal congestion received doses of 1, 2, 4, 4 and 4 mg of phenylephrine, and those with hypertension received 0.5, 1, 2 and 4 mg; a 0.25% solution was used for the 0.5- and 1-mg doses (two and four drops in each nostril respectively) and a 1% solution for the remainder. Less phenylephrine was given to the patients with hypertension because of concern about a possible rise in blood pressure; however, four of them received a second 4-mg dose. The usual recommended intranasal dose of phenylephrine is between 0.5 and 2 mg. The solutions were administered with a 50-μl Eppendorf pipette, with the patients semisupine. Immediately afterwards the patients turned their heads to the side of the nostril receiving the drop to maximize absorption. The blood pressure and heart rate were recorded in duplicate at 10-minute intervals for 60 minutes after each dose and for 120 minutes after the final dose.

The maximum alterations in mean blood pressure and heart rate were compared with baseline values obtained immediately prior to each dose by paired *t*-tests. As well, the changes in blood pressure and heart rate after each dose were assessed by analysis of variance of repeated measurements. Sample size calculations (by one-tailed tests, since there was no pharmacologic basis for expecting phenylephrine to cause a reduction in blood pressure, with $\alpha = 0.05$ and $\beta = 0.1$) showed that the 12 and 14 patients would be sufficient to detect minimum differences in mean blood pressure of 4.2 and 3.9 mm Hg respectively between the drug and placebo days. Lesser differences would not be clinically important.

Results

There were no significant increases in blood pressure following intranasal administration of phenylephrine in either group of patients (Tables I and II). Occasionally the mean blood pressure was slightly higher than the baseline value, but the differences were small and of no clinical importance. Similar fluctuations in blood pressure were seen following the intranasal administration of the placebo. The maximum increases in the diastolic pressure after administration of the placebo were 3.5 and 5.3 mm Hg for the group with nasal congestion and the group with hypertension respectively, 50 and 40 minutes after the 1-mg doses. Repeated instillation of phenylephrine did not result in a cumulative rise in the mean blood pressure in either group.

Alterations in heart rate after the administration of both phenylephrine and placebo were small, and at no time was the mean change significant. In particular, no phenylephrine-induced reflex bradycardia was observed.

In one patient with hypertension the blood pressure rose from 120/84 to 150/100 mm Hg 50 minutes after the first dose of phenylephrine (0.5 mg). However, there was a similar pressor response after the first dose of

Table I—Mean changes in blood pressure after intranasal administration of phenylephrine at hourly intervals to 12 patients with nasal congestion and normal blood pressure

Dose of phenylephrine (mg)	Blood pressure, systolic/diastolic (mm Hg)						
		Mean change after administration of phenylephrine; interval (min)					
	Baseline	10	20	30	40	50	60
1	118.5/71.5	−2.3/1.5	−1.1/3.4	−1.2/3.3	−1.8/3.3	−2.0/3.3	−2.3/3.8
2	116.3/74.5	0.9/0.4	0.7/1.9	1.3/2.7	2.3/1.3	1.8/2.3	3.3/2.8
4	119.6/77.3	5.0/0.5	3.0/−1.4	1.3/−2.1	0/−4.1	1.3/−2.7	0.8/−2.8
4	120.2/74.5	−0.6/−3.6	−1.3/−3.3	2.0/−2.3	−0.8/−1.5	−1.3/−2.3	−3.7/−1.8
4	116.5/73.1	2.3/−0.8	2.8/−2.1	1.6/0.1	1.0/0	3.3/1.4	1.5/1.5

Table II—Mean changes in blood pressure after intranasal administration of phenylephrine at hourly intervals to 14 patients receiving metoprolol for hypertension

Dose of phenylephrine (mg)	Blood pressure, systolic/diastolic (mm Hg)						
		Mean change after administration of phenylephrine; interval (min)					
	Baseline	10	20	30	40	50	60
0.5	136.8/85.6	−0.1/−1.4	0.9/−0.3	2.6/0.1	4.2/1.2	3.9/2.1	2.7/0.3
1	139.5/85.9	0.3/−1.1	−2.1/−1.4	−1.5/−1.1	−2.9/−3.6	−1.9/−5.5	−5.4/−7.6
2	129.0/78.2	2.0/−0.1	−0.1/0.9	−0.4/−0.1	1.3/0.5	2.4/1.5	3.4/1.0
4	132.4/79.2	1.3/3.7	0.4/1.0	1.1/2.2	−0.9/1.4	0.7/2.9	2.9/4.6

placebo, the pressure rising from 104/71 to 146/87 mm Hg by 60 minutes. Higher doses of the drug produced no changes in the blood pressure. The last four patients with hypertension to enter the study received an additional 4-mg dose of phenylephrine, so that the total dose administered was 11.5 mg. The extra dose did not affect the blood pressure or the heart rate.

None of the patients experienced adverse effects from either the phenylephrine or the placebo; in particular, no cardiac arrhythmias were noted.

Discussion

Although phenylephrine has been used as a nasal decongestant and a mydriatic for several decades, there is surprisingly little known about its systemic absorption and cardiovascular effects. It may be absorbed to some extent from the nasal mucosa, either directly, after instillation into the nasal cavity, or indirectly, as a result of drainage from the conjunctival sac following intraocular instillation. The currently accepted "safe" doses for intranasal or intraocular administration are based primarily upon descriptive data derived from observations in patients with a variety of conditions.

In 1949 Heath and Geiter[2] reported that phenylephrine did not alter the blood pressure of 120 patients receiving unstated doses in the conjunctival sac for mydriasis. More recently Kim and associates[3] instilled 15 to 40 mg of phenylephrine into the conjunctival sac of 12 patients with hypertension who were taking reserpine or guanethidine and 176 subjects with normal blood pressure; 15 control subjects with hypertension were given a placebo. The authors observed a mean increase in blood pressure (systolic/diastolic) of 30/13 mm Hg in the 12 patients with hypertension but no changes in blood pressure in the other two groups. These data are of limited value, however, since treatment was not randomized, some subjects underwent general anesthesia, and blood pressure measurements were taken from the case records. However, the results raise the possibility that sympathetic denervation with reserpine or guanethidine may result in α-adrenoceptor supersensitivity. In another study intranasal administration of phenylephrine (1.25 to 6.0 mg) to 46 patients with rhinologic conditions and concurrent hypertension, diabetes or cardiac or thyroid disease produced no alterations in blood pressure.[4] Similar negative findings have been reported for oxymetazoline, another vasoconstricting α-adrenoceptor agonist, in 99 patients with nasal congestion.[5] In contrast, several anecdotal reports have described possible pressor reactions to phenylephrine instilled in the conjunctival sac.[1,6-9]

The absence of data from rigorously designed clinical trials and the widespread use of phenylephrine by persons with normal or high blood pressure led us to undertake this study. We found that the intranasal administration of 7 to 30 times the usual dose of phenylephrine to patients with nasal congestion but normal blood pressure produced no significant changes in blood pressure or heart rate. Since phenylephrine absorption could be increased when the nasal mucosa is edematous and vascular, this lack of a pressor response to a cumulative dose of 15 mg of phenylephrine administered by a standard technique under supervision suggests that patients would have to use considerably more phenylephrine intranasally on their own to exhibit cardiovascular effects. The degree of systemic absorption from the nasal mucosa is likely small, since doses of 1 to 1.5 mg infused intravenously over 5 minutes will produce a pressor response.[10]

Patients receiving β-blocker therapy for hypertension may be especially susceptible to marked increases in blood pressure following the topical application of vasoconstricting agents,[1,11] for β-adrenoceptor blockade may reduce the vasodilating tendencies of the arteriolar smooth muscle, allowing unopposed α-receptor activity and a pressor response. Administration of a β-adrenoceptor agonist such as isoproterenol will predictably result in vasodilatation by decreasing the tone of vascular smooth muscle. However, under normal physiologic conditions the α-adrenoceptor appears to be the main determinant of vascular tone. Stimuli such as assumption of the erect position lead to increases in sympathetic activity, arteriolar vasoconstriction and the maintenance of blood pressure.[12] The vasodilating effects of the β-adrenoceptor are usually seen following epinephrine release from the adrenal glands, as during psychologic stress[13] and hypoglycemia.[14] Also, β-blockade in both anesthetized dogs[15] and humans[16] does not seem to result in supersensitivity of the α-adrenoceptor after the administration of relatively pure α-receptor agonists, such as norepinephrine and methoxamine.

In our 14 patients receiving metoprolol for hypertension there was no change in blood pressure or heart rate following intranasal administration of phenylephrine in doses higher than recommended. One patient exhibited an increase in blood pressure after the first dose, 0.5 mg, but this also occurred after the first dose of placebo. This observation underscores the possibility of spurious phenylephrine–β-blocker interactions: the usual daily variations in blood pressure might simulate a drug-induced pressor effect.

Metoprolol is a relatively cardioselective β-adrenoceptor antagonist: it blocks the cardiac β_1-receptor somewhat more than the β_2-receptors of the lung and peripheral vasculature.[17] This preferential blockade is apparent only at low doses. The mean daily dose of 185.7 mg taken by the patients in this study would have resulted in substantial β-adrenoceptor antagonism.[18] None the less, it would be unwise to extrapolate our findings to patients with hypertension treated with nonselective β-blockers, such as propranolol, since these may cause even more inhibition of the vascular β_2-adrenoceptor. Our findings do suggest that patients with hypertension receiving cardioselective β-blocker therapy are not predisposed to clinically important increases in blood pressure following topical administration of phenylephrine in the usually recommended doses.

There have been at least two reports of increases in systemic blood pressure following oral administration of preparations containing vasoconstricting substances. In healthy volunteers with normal blood pressure small but statistically significant increases in blood pressure followed ingestion of high doses (120 and 180 mg) of pseudoephedrine, an α-adrenoceptor agonist.[19] Increases in blood pressure were also noted in similar subjects

receiving phenylpropanolamine orally in the treatment of anorexia or nasal congestion.[20]

Clearly, α-adrenoceptor agonists may increase the blood pressure if sufficient amounts reach the systemic circulation. There is little evidence that the doses of phenylephrine recommended for topical intranasal use alter the systemic blood pressure with or without concurrent β-blocker therapy. However, since larger amounts of phenylephrine have been used in clinical practice for mydriasis, the "safe" dose should be established in controlled clinical trials with subjects whose blood pressure is normal and in patients receiving β-blocker therapy for hypertension.

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Torsades de pointes, a common arrhythmia, induced by medication

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Between May 1980 and April 1981 four patients were referred to one hospital with syncope or recurrent ventricular fibrillation while taking antiarrhythmic or phenothiazine drugs. In all the patients ventricular tachyarrhythmias with the characteristics of torsades de pointes were documented in association with prolonged QT intervals. With removal of the offending agent (in all the patients) supplemented by temporary overdrive pacing (in two patients) the tachyarrhythmias subsided. This study suggests that drug-induced torsades de pointes is an important clinical entity that occurs more frequently than has been suspected.

Entre mai 1980 et avril 1981 quatre patients ont été reçus en consultation à un hôpital souffrant de syncope ou de fibrillation ventriculaire récidivante alors qu'ils prenaient des médicaments antiarythmiques ou des phénothiazines. Chez tous ces patients on a vérifié des tachyarythmies ayant les caractéristiques de torsades de pointes en association avec une prolongation de l'intervalle QT. Le retrait de la médication responsable (chez tous les patients) et l'addition temporaire d'une stimulation électrosystolique rapide (chez deux patients) ont amené la résolution des tachyarythmies. Cette étude indique que les torsades de pointes provoquées par les médicaments représentent une entité clinique importante qui survient plus souvent qu'on ne l'avait soupçonné.

Ignorance is not so damnable as humbug, but when it prescribes pills it may happen to do more harm.

—George Eliot[1]

In 1967 Dessertene[2] used the term "torsades de pointes" (twisting of the points) to describe a bizarre form of ventricular tachycardia with unique morphologic features. The tachycardia was characterized by alternating cycles of electrical polarity with progressive sinusoidal changes in the amplitude of successive ventricular

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